Overview of the Draft Ethylene Oxide (EtO) Carcinogenicity Assessment for the Science Advisory Board December 8, 2006

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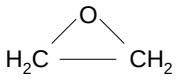
Background

- EPA last published a human health effects assessment of the potential carcinogenicity of ethylene oxide (EtO) in 1985
- Office of Research and Development (ORD) has completed a draft evaluation of the more recent database on the carcinogenicity of EtO
- This draft assessment evaluates the potential cancer risk from inhalation exposure to EtO
- The assessment is relevant to the needs of the Office of Air, which is responsible for regulating air emissions of EtO, and to the Office of Pesticides Programs, which is responsible for regulating the use of EtO for pesticide applications

EtO Exposure



- Gas at room temperature
- Used primarily as a chemical intermediate; also used as sterilizing agent for medical equipment and as fumigating agent for spices
- Largest sources of human exposure are in occupations involving contact with the gas
- General population exposures, e.g., in areas near production or sterilizing/fumigating facilities, are also of potential concern
- EtO is not persistent in the environment

Summary of Draft Findings

1. Unequivocal evidence of cancer in rodents
2. Strong evidence in humans
3. Weight-of-evidence evaluation supports mutagenic mode of action for rodents and humans
4. Hazard characterization: “carcinogenic to humans” based on mechanistic evidence (with less than sufficient human evidence)
5. Primary cancer risk estimate based on linear modeling of lymphohematopoietic cancer data on males in large NIOSH study and linear low-dose extrapolation, which is supported by clear evidence of mutagenicity

Summary of Draft Findings, continued

6. Because of mutagenic mode of action, increased early-life susceptibility should be assumed and age-dependent adjustment factors applied, in accordance with EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens*
7. Considered, but rejected, the use of quadratic dose-response function
8. Additional models and datasets were also considered
9. Different models used for risk estimates for occupational exposure levels (to support OPP efforts for pesticide applications)

Unequivocal Evidence of Cancer in Rodents

- Clear evidence for multiple cancer responses in multiple species
- Two inhalation studies of F344 rats
  - male rats: mononuclear cell leukemias in the spleen, peritoneal mesotheliomas in the testes, brain tumors
  - female rats: mononuclear cell leukemias in the spleen, brain tumors
- One inhalation study (NTP) of B6C3F1 mice
  - male mice: lung carcinomas
  - female mice: lung carcinomas, malignant lymphomas, uterine adenocarcinomas, mammary gland adenocarcinomas

Strong Evidence of Lymphohematopoietic Cancer in Humans

- 10 of 11 epidemiologic studies suggest possible increased risk
- Strongest evidence from large NIOSH mortality study (2004)
  - largest study by far - 18,254 workers, mostly sterilizer workers
  - 55% female, 45% male
  - relatively long follow-up period - 27 years on average
  - individual exposure estimates for all workers
  - exposure to other chemicals considered insignificant
  - statistically significant exposure-response trends observed in males for all lymphohematopoietic cancers and for lymphoid cancers (NHL, lymphocytic leukemia, and myeloma); no evidence in females

More Limited Evidence of Breast Cancer in Humans

- Primarily from large NIOSH mortality (2004) and incidence (2003) studies
  - statistically significant exposure-response trend observed in mortality study
  - incidence study of sub-cohort of 7,576 women (from the larger NIOSH study); 5,139 with interviews
    - significant exposure-response trends in both full study group and subgroup with interviews
    - in subgroup with interviews, numerous potential confounders were examined; important factors were accounted for in the exposure-response analyses
- Some supporting evidence from a few smaller studies

Mutagenic Mode of Action (for all tumor types)

- Key events: DNA adduct formation and the resulting genetic damage
- EtO is a direct-acting alkylating agent
- Numerous studies have shown that EtO forms protein (hemoglobin) and DNA adducts in mice and rats
  - exposure-response relationships for adduct formation
  - DNA adducts are observed in tissues throughout the body, including lung, brain, kidney, spleen, liver, testes
- Several studies of humans have reported exposure-response relationships between hemoglobin adduct levels and EtO exposure levels
- Incontrovertible evidence that EtO is mutagenic from numerous *in vitro* and *in vivo* assays
- EtO induces a variety of mutagenic and genotoxic effects, including chromosome breaks, micronuclei, sister chromatid exchanges, and gene mutations; some observed in humans
- These genetic effects occur in the absence of cytotoxicity or other overt toxicity
- We are not aware of any alternative or additional modes of action for EtO carcinogenicity

Hazard Characterization: upgrade to "carcinogenic to humans" based on mechanistic evidence with (less than sufficient human evidence)

Evidence satisfies the conditions for "carcinogenic to humans" in EPA's 2005 *Guidelines for Carcinogen Risk Assessment*:

1. Strong evidence of cancer in humans associated with EtO exposure
2. Extensive evidence of EtO-induced carcinogenicity in laboratory animals (including lymphohematopoietic cancers in rats and mice and mammary carcinomas in mice, the same cancers observed in human studies)
3. Mode of action identified in laboratory animals (mutagenic mode of action; see above)
4. Strong evidence that key precursor events are anticipated to occur in humans and progress to tumors (increased levels of genotoxicity have been observed in human populations exposed to EtO)

Potentially More Susceptible Lifestages or Subpopulations

- Because of EtO's mutagenic mode of action, and in the absence of chemical-specific data regarding early-life susceptibility, increased early-life susceptibility should be assumed in accordance with EPA's 2005 *Supplemental Guidance*
- People with DNA repair deficiencies or genetic polymorphisms conveying a decreased efficiency in detoxifying enzymes may have increased susceptibility to EtO carcinogenicity

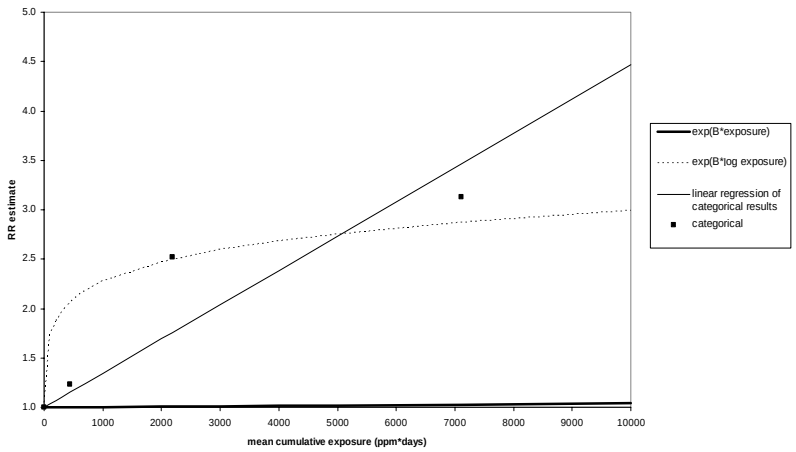
Cancer Risk Estimates Based on Human Data from NIOSH Study

- Human data preferred to rodent data when adequate human data are available
- Other epidemiologic studies much smaller, with less reliable exposure estimates and possible co-exposures to other chemicals
- From NIOSH study, modeled lymphohematopoietic cancers in males and breast cancer in females
- Linear dose-response model used to get "point of departure" (PoD; 1% extra risk)
- Linear extrapolation used below PoD; supported by mutagenic mode of action
- Alternative estimates derived using different models/datasets from NIOSH study and rodent bioassays for comparison

Cancer Risk Estimates Derived from Multiple Analyses/Datasets: Epidemiological Data

- NIOSH study data for lymphohematopoietic cancer and breast cancer modeled with linear and nonlinear (i.e., supra-linear and sub-linear) models (see next slide)
  - Sub-linear model does not fit overall data, which have an underlying supra-linear exposure-response relationship; particularly divergent in low-exposure range of interest
  - Supra-linear model is best-fitting, but probably too steep in low-exposure range
  - Linear model (of categorical data with highest exposure group excluded) preferred for low-exposure range of the data

Figure. RR estimate for lymphohematopoietic cancer in males vs. mean exposure (from Steenland et al., 2004, Table 6, Cox regression results, except for linear regression [see text]; log and categorical exposures with 15-year lag), unadjusted for continuous exposure. (Highest categorical exposure quartile not shown.)



Cancer Risk Estimates Derived from Multiple Analyses/Datasets: Epidemiological Data cont.

- For lymphohematopoietic cancer, estimates derived for all lymphohematopoietic cancer and for subcategory of "lymphoid" cancers
  - Lymphohematopoietic preferred because:
    - Misclassification or non-classification of tumor type is more likely to occur for subcategories of lymphohematopoietic cancers than for the overall category (e.g., 4 of the 25 leukemias were not specified)
    - "Lymphoid" category did not include Hodgkin's lymphoma, which also exhibited evidence of exposure-response trends
- For breast cancer, estimates derived for full cohort and sub-cohort with interviews, and for invasive and *in situ* tumors combined and invasive tumors only
  - Sub-cohort estimates preferred because:
    - There was under-ascertainment of incident cases in the full cohort
    - Information on other breast cancer risk factors was obtained only for the sub-cohort with interviews
- Estimates derived for cancer mortality and incidence

Cancer Risk Estimates Derived from Multiple Analyses/Datasets: Rodent Data

- Cancer risk estimates derived from all 3 bioassays for tumor sites individually (by sex/species/bioassay) and combined (within sex/species/bioassay)

Adjustment for Increased Early-Life Susceptibility

- Based on the conclusion that EtO is carcinogenic by a mutagenic mode of action, increased early-life susceptibility is assumed
  - in accordance with EPA's 2005 *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens*
- In the absence of chemical-specific data on early-life susceptibility, the *Supplemental Guidance* recommends application of default age-dependent adjustment factors (ADAFs)
- Calculations of lifetime cancer risks using the ADAFs are presented
- Default ADAFs might not be appropriate for breast cancer, which appears to have a different age profile for early-life susceptibility (e.g., increased susceptibility during puberty)

Cancer Risk Estimates for Occupational Exposures

- Not commonly done in EPA risk assessments; however occupational exposure levels of concern to EPA when EtO used as a pesticide
- Based on NIOSH results for lymphohematopoietic cancers in males and breast cancer in females
- Different exposure-response models (best-fitting "supra-linear" models) used to represent exposure-response relationships at higher exposures

Ethylene Oxide Industry Council (EOIC) Risk Estimates (Kirman et al., 2004)

- Risk estimates (for leukemia mortality only) based on quadratic (dose-squared) model and combined data from NIOSH 1993 and smaller Union Carbide 1993 studies
- Assumes leukemias are due to chromosome translocations and that these require 2 independent chromosome breaks and, thus, leukemias should be modeled with a dose-squared model
- These investigators also conclude that combined epidemiologic data support quadratic model

Discussion of EOIC Estimates

- Evidence exists that challenges the assumption that chromosome translocations are the sole initiating events for leukemias
  - Point mutations relevant to carcinogenesis in general (e.g., in the p53 and N-*ras* genes), and leukemogenesis in particular (e.g., in the AML1 gene in AML and in the BCL6 gene in NHL), are also observed in human leukemias
  - Translocations are often later-occurring events in carcinogenesis, resulting from genomic instability
- Even for translocations, a "two-hit" model for EtO is not compulsory
  - Even if two reactions with DNA are early events in some EtO-induced lymphohematopoietic cancers, it is not necessary that both events be associated with EtO exposure
  - EtO could also produce translocations indirectly by forming DNA or protein adducts that affect the normally-occurring recombination activities of lymphocytes or the repair of spontaneous double-strand breaks
- The empirical evidence does not support a quadratic model
  - Data from more recent NIOSH update (2003, 2004), with longer follow-up time and more cases, not consistent with quadratic model
  - Several studies of translocation frequencies find these to be linear with dose

Comparison of inhalation unit risk estimates for cancer

	Based on human data	
U.S. EPA (this document)	Lymphohematopoietic cancer incidence[a]	9.0×10^{-4} (:g/m^3)$^{-1}$ [b]
	Breast cancer incidence[c]	5.0×10^{-4} (:g/m^3)$^{-1}$
Ethylene Oxide Industry Council (Kirman et al., 2004)	Leukemia mortality	4.5×10^{-8} (:g/m^3)$^{-1}$ Range of 1.4×10^{-8} (:g/m^3)$^{-1}$ to 1.4×10^{-7} (:g/m^3)$^{-1}$ [d]
	Based on rodent data	
U.S. EPA (this document)	Female mouse tumors	4.6×10^{-5} (:g/m^3)$^{-1}$
U.S. EPA (this document)	all rodent data	Range of 2×10^{-5} (:g/m^3)$^{-1}$ to 5×10^{-5} (:g/m^3)$^{-1}$
California EPA (CalEPA, 1999)	Mononuclear cell leukemia in female rats	8.8×10^{-5} (:g/m^3)$^{-1}$
Health Canada (Health Canada, 2001)[e]	Mononuclear cell leukemia in female rats	3.3×10^{-5} (:g/m^3)$^{-1}$
Ethylene Oxide Industry Council (Kirman et al., 2004)	Mononuclear cell leukemia in rats and lymphomas in mice	Range of 2.6×10^{-8} (:g/m^3)$^{-1}$ to 1.5×10^{-5} (:g/m^3)$^{-1}$ [f]

[a] Estimate based on lymphohematopoietic cancer mortality is 5.0×10^{-4}(:g/m^3)$^{-1}$.
[b] Unadjusted for assumed increased early-life susceptibility.
[c] Estimate based on breast cancer mortality is 2.8×10^{-4} (:g/m^3)$^{-1}$.
[d] Estimates based on linear extrapolation from EC0001 - EC000001 obtained from the quadratic model; Kirman et al. also report unit risk estimate of 4.5×10^{-7} (:g/m^3)$^{-1}$ from a linear model.
[e] WHO (2003) presents the same quantitative risk estimates for cancer as Health Canada (2001), Health Canada having provided the first draft of WHO's assessment
[f] Estimates based on linear and quadratic models with various points of departure

Characterization of Uncertainty in the Carcinogenicity Assessment Document

- Qualitative discussion of weight of evidence for hazard characterization (Section 3.5.1)
- Strengths and limitations of epidemiologic studies discussed extensively in Appendix A and summarized in Section 3.1
- Extensive qualitative discussion of uncertainties in cancer risk estimates (Section 4.1.3)
- Comparisons with risk estimates from other assessments/publications (Sections 4.4.1 and 4.4.2)
- Multiple analyses/datasets explored (sensitivity analysis with respect to different assumptions) (Section 4)
- MLEs and upper bounds of risk are calculated (Section 4.3)

Charge Questions for the SAB Ethylene Oxide Review Panel

The panel is requested to evaluate the scientific validity of EPA's carcinogenicity assessment.

The specific charge questions that the panel is asked to address are listed on the following six slides.

Charge Questions: Carcinogenic Hazard

1. Do the available data and discussion in the draft document support the hazard conclusion that EtO is carcinogenic to humans based on the weight-of-evidence descriptors in EPA's 2005 *Guidelines for Carcinogen Risk Assessment*? In your response, please include consideration of the following:

   1.a EPA concluded that the epidemiological evidence on EtO carcinogenicity was strong, but less than completely conclusive. Does the draft document provide sufficient description of the studies, balanced treatment of positive and negative results, and a rigorous and transparent analysis of the data used to assess the carcinogenic hazard of ethylene oxide (EtO) to humans? Please comment on the EPA's characterization of the body of epidemiological data reviewed. Considerations include:

      a) the consistency of the findings, including the significance of differences in results using different exposure metrics, b) the utility of the internal (based on exposure category) versus external (e.g., SMR and SIR) comparisons of cancer rates, c) the magnitude of the risks, and d) the strength of the epidemiological evidence.

Charge Questions: Carcinogenic Hazard

1.b. Are there additional key published studies or publicly available scientific reports that are missing from the draft document and that might be useful for the discussion of the carcinogenic hazard of EtO?

1.c. Do the available data and discussion in the draft document support the mode of action conclusions?

1.d. Does the hazard characterization discussion for EtO provide a scientifically-balanced and sound description that synthesizes the human, laboratory animal, and supporting (e.g., *in vitro*) evidence for human carcinogenic hazard?

Charge Questions: Risk Estimation

2. Do the available data and discussion in the draft document support the approaches taken by EPA in its derivation of cancer risk estimates for EtO? In your response, please include consideration of the following:

2.a. EPA concluded that the epidemiological evidence alone was strong but less than completely conclusive (although EPA characterized the total evidence - from human, laboratory animal, and *in vitro* studies - as supporting a conclusion that EtO as "carcinogenic to humans"). Is the use of epidemiological data, in particular the Steenland et al. (2003, 2004) data set**,** the most appropriate for estimating the magnitude of the carcinogenic risk to humans from environmental EtO exposures? Are the scientific justifications for using this data set transparently described? Is the basis for selecting the Steenland et al. data over other available data (e.g., the Union Carbide data) for quantifying risk adequately described?

Charge Questions: Risk Estimation

2.b. Assuming that Steenland et al. (2003, 2004) is the most appropriate data set, is the use of a linear regression model fit to Steenland et al.'s categorical results for all lymphohematopoietic cancer in males in only the lower exposure groups scientifically and statistically appropriate for estimating potential human risk at the lower end of the observable range? Is the use of the grouping of all lymphohematopoietic cancer for the purpose of estimating risk appropriate? Are there other appropriate analytical approaches that should be considered for estimating potential risk in the lower end of the observable range? Is EPA's choice of a preferred model adequately supported and justified? In particular, has EPA adequately explained its reasons for not using a quadratic model approach such as that of Kirman et al. (2004) based? What recommendations would you make regarding low-dose extrapolation below the observed range?

Charge Questions: Risk Estimation

2.c. Is the incorporation of age-dependent adjustment factors in the lifetime cancer unit risk estimate, in accordance with EPA's Supplemental Guidance (U.S. 2005b), appropriate and transparently described?

2.d Is the use of different models for estimation of potential carcinogenic risk to humans from the higher exposure levels more typical of occupational exposures (versus the lower exposure levels typical of environmental exposures) appropriate and transparently described in Section 4.5?

2.e. Are the methodologies used to estimate the carcinogenic risk based on rodent data appropriate and transparently described? Is the use of "ppm equivalence" adequate for interspecies scaling of EtO exposures from the rodent data to humans?

Charge Questions: Uncertainty

3. EPA's *Risk Characterization Handbook* requires that assessments address in a transparent manner a number of important factors. Please comment on how well this assessment clearly describes, characterizes and communicates the following:

   a. The assessment approach employed;

   b. The use of assumptions and their impact on the assessment;

   c. The use of extrapolations and their impact on the assessment;

   d. Plausible alternatives and the choices made among those alternatives;

   e. The impact of one choice versus another on the assessment;

   f. Significant data gaps and their implications for the assessment;

   g. The scientific conclusions identified separately from default assumptions and policy calls;

   h. The major risk conclusions and the assessor's confidence and uncertainties in them, and;

   i. The relative strength of each risk assessment component and its impact on the overall assessment.

Ethylene Oxide Assessment Acknowledgements

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